

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re of Application of: YOUNG, et al.
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For: METHODS FOR IDENTIFYING MODULATORS OF N-TYPE ION
CHANNEL INACTIVATION
Confirmation No.: Not yet assigned
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Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

IN THE CLAIMS:

Please cancel claims 1-44.

Please add new claims 45-51 as follows:

45. A method of evaluating a compound for the ability to inhibit binding of an intracellular receptor region of an α -subunit of a voltage-gated ion channel and an amino-terminal inactivation region of an ion channel protein, wherein the ion channel protein is a potassium channel protein selected from the group consisting of Kv β 1, Kv β 1.2, Kv β 1.3, Kv1.4, and Kv3.4, comprising:
- a) providing a first peptide selected from the group consisting of an isolated potassium channel α -subunit, an isolated intracellular receptor region, and a biologically active fragment of said α -subunit;
 - b) providing a second peptide selected from the group consisting of an isolated beta cytoplasmic ion channel protein, an isolated amino-terminal inactivation region, and a biologically active fragment of said cytoplasmic protein;
 - c) contacting said first peptide and said second peptide with said compound; and
 - d) determining the ability of said compound to interfere with the binding of said first peptide with said second peptide, wherein a decrease in said binding in the presence of said compound compared to said binding in the absence of said compound indicates that said compound inhibits binding of said intracellular receptor region to said amino-terminal inactivation region.
46. The method of claim 45, wherein the voltage-gated channel protein is a potassium channel protein selected from the group consisting of Kv1.1, Kv1.2, Kv1.3, Kv1.4, Kv1.5, Kv1.6, and Kv3.4.
47. A method of screening a candidate compound for the ability to inhibit binding of an intracellular receptor region of an α -subunit of a voltage-gated ion channel to an amino-terminal inactivation region of an ion channel protein, comprising:

- a) adding said candidate compound to a modified host cell comprising a reporter gene; and
 - b) monitoring expression of said reporter gene, wherein a decrease in expression is an indication that said candidate compound inhibits binding of the intracellular receptor region of the α -subunit to the amino-terminal inactivation region of the ion channel protein.
48. The method of claim 47, wherein the voltage-gated ion channel is a potassium channel protein selected from the group consisting of Kv1.1, Kv1.2, Kv1.3, Kv1.4, Kv1.5, Kv1.6, and Kv3.4.
49. The method of claim 47, wherein the amino-terminal inactivation region is an amino-terminal domain of a potassium channel protein selected from the group consisting of Kv β 1, Kv β 1.2, Kv β 1.3, Kv β 3, Kv1.4, and Kv3.4.
50. A method for identifying compounds which inhibit N-type inactivation of a voltage-gated ion channel, comprising:
- a) administering a compound to a modified host cell comprising:
 - i) a first hybrid protein comprising a DNA-binding domain of a transcriptional activator in polypeptide linkage to either 1) an intracellular receptor region of an α -subunit of a voltage-gated ion channel; or 2) an amino-terminal inactivation region of an ion channel protein;
 - ii) a second hybrid protein comprising an activation domain of a transcriptional activator in polypeptide linkage to said intracellular receptor region if said DNA-binding domain is in polypeptide linkage to said amino-terminal inactivation region or to said amino-terminal inactivation region if said DNA-binding domain is in polypeptide linkage to said intracellular receptor region; and
 - iii) a reporter gene whose transcription is dependent upon the first hybrid protein and the second hybrid protein being bound to each other, thereby reconstituting a transcriptional activator;
 - b) incubating the modified host cell for a suitable period;
 - c) determining whether the administration of the compound inhibits expression of the reporter gene; and
 - d) identifying a compound which inhibits expression of the reporter gene as an inhibitor of N-type inactivation of said voltage-gated ion channel.
51. A modified host cell comprising:
- a first hybrid protein comprising an intracellular receptor region of an α -subunit of a voltage-gated ion channel in polypeptide linkage to a first peptide of a peptide binding pair; and
 - a second hybrid protein comprising an amino-terminal inactivation region of an ion channel protein in polypeptide linkage to a second peptide of the peptide binding pair, wherein binding interaction between the first peptide and the second peptide in the modified host cell causes activation of a signal transduction pathway in said modified host cell.

REMARKS

The claims are 45-51. The current claims are identical to the claims allowed in the parent application (USSN 09/295,999), other than minor typographical corrections. Therefore, Applicant respectfully requests that these claims be passed to issue.


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